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Periodontal infections: understanding the complexity – Consensus of the Seventh European Workshop on Periodontology

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Abstract

Introduction: Periodontal diseases are the pathological manifestation of the host response against the bacterial challenge from the dental biofilm at the tooth/gingival interface. The remit of this working group was to update the existing knowledge on the infectious nature of periodontal diseases.

Material and Methods: The literature was systematically searched and critically reviewed. Four manuscripts were produced in specific topics identified as key areas to understand the importance of the microorganisms in the etio-pathogenesis of periodontal diseases.

Results/Conclusions: The results and conclusions of the review process are presented in the following papers, together with the group consensus statements aiming to answer the following questions: (1) Has the use of molecular methods for the characterization of the human oral microbiome changed our understanding of the role of bacteria in the pathogenesis of periodontal disease process? (2) Are the periodontal microbial complexes associated with specific cell and tissue responses? (3) How is the development of dental biofilms influenced by the host? (4) What can we learn about biofilm/host interactions from the study of inflammatory bowel disease? This consensus report provides answers to these questions with the most updated information on periodontal microbiology

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Consensus Report

Periodontal diseases are the pathological manifestation of the host response against the bacterial challenge from the dental biofilm at the tooth/gingival interface.

- Plaque-induced gingivitis is a chronic inflammatory response to the accumulation of supragingival biofilm.

- Periodontitis is a chronic inflammatory disease that results from a complex polymicrobial infection, leading to tissue destruction as a consequence of the perturbation of the homeostasis between the subgingival microbiota and the host defenses in susceptible individuals. This bacterially driven

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disease may be considered to differ from an accepted definition of infection (i.e. invasion by and multiplication of pathogenic microorganisms in a body part or tissue which may produce subsequent tissue injury and progress overt disease through a variety of cellular or toxic mechanisms).

Research into the microbiota of other body mucosal surfaces has demonstrated important benefits to the host due to activity of the resident bacteria. Evidence is emerging that the resident oral microbiota delivers similar benefits to the host.

The study of periodontal health-associated oral biofilms, as well as their interaction with the local tissues, will allow us to understand the potential protective mechanisms and define preventive strategies.

Microbiological studies assessing a comprehensive description of the composition and function of the oral microbiota may allow us to identify bacterial signatures of relevance to microbial diagnostic approaches and therapeutic targets.

The study of the complex interactions between the subgingival microbiota and the ulcerated epithelium at the tooth-gingival interface allows the study of host microbial interactions, which may help the understanding of other complex mucosal infection.

The mouth is a reservoir of microorganism with the potential to cause disease in other body sites. The in-depth knowledge of the characteristics and virulence factors of these potential pathogens will help the understanding of the pathogenesis and management of these infections.

Has the Use of Molecular Methods for the Characterization of the Human Oral Microbiome (HOM) Changed our Understanding of the Role of Bacteria in the Pathogenesis of Periodontal Disease Process?

Wade, W.G. (Wade 2011)

1. How has the introduction of molecular microbiology changed our understanding on the role of established (World Workshop on Periodontology, 1996) periodontal pathogens as defined by the classic Socransky criteria?

The use of molecular techniques such as DNA/DNA checkerboard analysis, cloning, etc. has further emphasized the association of the classic periodontal pathogens with periodontitis, introducing the possible role as putative pathogens of additional species such as

Eubacterium nodatum, *Porphyromonas endodontalis*, *Prevotella tannerae*, *Filifactor alocis* or *Treponema denticola*. The introduction of molecular ecology techniques has expanded our knowledge stressing the high species richness of the subgingival microbiota and the possible importance of yet uncultivable bacteria that being associated with diseased sites deserve further investigation in their role as periodontal pathogens.

2. How may the increased knowledge on the composition of the subgingival microbiota improve our understanding of the pathogenesis, diagnosis and treatment of periodontitis?

This increased awareness of a higher diversity and complexity in the subgingival microbiota indicates the possibility of identifying new pathogenic species or communities, however this new information has not yet impacted our current diagnosis and treatment. The current molecular technology provides us with new resources to identify not only single microorganisms, but communities with potential pathogenic importance. Moreover, the impact of genomic sequencing has shown the extreme variability of the genomes of strains within a given species, which stresses the importance of individual genes encoding virulence factors (function) rather than solely the presence and levels of particular species.

3. What is the role of as yet uncultured bacteria identified by DNA sequencing alone?

The role of yet uncultured phylotypes in oral biofilms is unknown at present due to our inability to culture them, but it is possible to predict their likely activities and functions by comparison with related members of the subgingival biofilm, based on their phylogenetic position. In addition, Fluorescence In Situ hybridization studies have confirmed the presence and viability of yet uncultured phylotypes in oral biofilms.

4. What is the role of culture-based microbiology versus molecular methods in our current and future understanding of the importance of bacteria in periodontitis?

Culture-based microbiology is essential to understand the properties of these new yet uncultured bacteria, in health and disease. If we are able to grow them, we can study them both in vitro and in vivo situations, and determine antimicrobial susceptibility. There is a need to study these bacteria not only as single species, but also as a consortium and investigate their interactions with

human cells and host tissues. There is a clear need to combine the culture-based and molecular techniques to gain full understanding of the complexity of the subgingival microbiota.

5. How will the development of the HOM database change our views in periodontal microbiology? How does this oral database relate to research in other chronic infections?

When the full genome sequences of the majority of oral bacteria are available, it will be feasible to screen for genes encoding virulence factors and other relevant functions. The HOM is the best characterized of the microbiomes associated with human body sites and it is a useful resource to add to the expanding databases. It has the potential to enhance future diagnostic and therapeutic applications.

Periodontal Microbial Complexes Associated with Specific Cell and Tissue Responses

Moritz Kebschull and Panos N. Papapanou (Kebschull & Papapanou 2011)

1. What is the evidence to support a specific host-tissue response to colonization by specific microbiota?

The limited number of cross-sectional studies in humans to date has demonstrated that different microbial profiles are associated with distinct host tissue responses (transcriptomic responses in gingival tissues and proteomic profiles in gingival crevicular fluid) even in tissues with similar clinical presentation. These results are in line with extensive in vitro studies and a number of animal studies that demonstrated that different microorganisms elicit distinctive host-responses.

Hence, heterogeneous patho-physiological pathways may lead to similar clinical presentation. At present, there is no single host response signature for disease progression (consistent with extensive biomarker analysis).

2. Do different microbial species elicit specific host responses resulting in tissue destruction?

Experimental animal studies have shown that distinct microorganisms result in different rates of bone loss. Furthermore, combinations of periodontal bacterial species have been shown to have synergistic effects on tissue destruction.

In vitro studies also demonstrated additive, synergistic, or antagonistic

effects of combinations of different bacteria when compared with corresponding mono-infections, resulting in altered cellular responses with respect to cytokine production and apoptosis. Furthermore, mono-infections with different species have been shown to elicit cellular responses, which are consistent with in vivo mechanisms of tissue destruction.

3. What is the clinical relevance of the differences in host-parasite interactions?

Evidence from experimental and human studies has shown a direct influence of different bacterial complexes on gene and protein expression in periodontal tissues and conceivably on clinical phenotypes.

This findings has not yet been explored in terms of clinical application, but the clinical relevance of understanding the microbial composition of the periodontal pockets is supported by at least three longitudinal studies (van der Velden et al. 2006, Fine et al. 2007, Haubek et al. 2008) in which colonization with specific subgingival bacteria (*Aggregatibacter actinomycetemcomitans*) and/or clonal types showed an increased risk of onset and rate of progression of disease.

How is the Development of Dental Biofilms Influenced by the Host?

Philip D. Marsh and Deirdre A. Devine (Marsh & Devine 2011)

1. What is the impact of the ecological factors on the characteristics of the supragingival and subgingival biofilms?

All microbial communities are shaped by both physical and biological factors.

For example, a change in the availability of nutrients, pH and redox potential of the site can alter the overall composition of the biofilm. In addition, lifestyle factors, such as diet, smoking, general health and oral hygiene practice, can act as modifiers of the characteristics of the biofilms.

2. What is the impact of other oral biofilms on the microbiota of the tooth/gingival interface?

Biofilms on other oral surfaces harbor microorganism associated with periodontal diseases and may act as a reservoir for the tooth-gingival interface.

3. What is the role of person-to-person transmission in the composition of the oral microbiota?

In young children, vertical transmission from the mother or primary

care giver is a major factor in the development of the oral microbiota, and this may include periodontal pathogens. There is evidence that *P. gingivalis* and *A. actinomycetemcomitans* can be transmitted from adult to adult.

4. Can we explain the geographical differences in the composition of the subgingival biofilm?

Geographical differences in the composition of the subgingival biofilm have been reported. To date, there is insufficient data to explain the basis of these differences. New studies are needed to address this issue, including the application of new technologies and the evaluation of the whole microbiota.

5. Are the subgingival microbial changes associated with periodontitis the result of colonization by exogenous microorganisms and by the overgrowth of resident microbiota due to ecological changes?

The resident oral microbiota is diverse and complex, and includes bacteria associated with periodontal health and disease. However, certain periodontal pathogens can be detected in the subgingival environment in healthy subjects, but infrequently and in low numbers. They may be acquired by vertical and horizontal transmission, but the chronology of the acquisition is currently unknown. Changes in the environment (bacterial- or host-induced) may alter the ecological competition between the potential pathogenic and beneficial bacterial species, altering the composition of the subgingival microbiota, and hence unbalancing the health-associated host biofilm homeostasis, triggering periodontitis.

6. Which strategies could be applied to influence the composition of the tooth-associated biofilm, so that it is compatible with periodontal health?

Effective oral hygiene practices, that involve regular disruption of supragingival biofilm, are capable of maintaining a biofilm with a composition that is compatible with periodontal health, in the majority of subjects.

Adjunctive chemical agents that reduce plaque formation and/or gingival inflammation (thereby preventing environmental changes that promote the growth of periodontal pathogens) may be valid strategies.

Mechanical and chemical strategies could target non-dental biofilms that may act as reservoirs of potential periodontal pathogens for tooth colonization.

Potential strategies could be aimed at altering the formation, ecology or structure of the biofilm, such as reducing bacterial adherence, changing the extracellular matrix, altering quorum sensing, regulating the expression of virulence factors, etc.

What Can We Learn about Biofilm/Host Interactions from the Study of Inflammatory Bowel Disease (IBD)?

Amedeo Indriolo, Salvatore Greco, Paolo Ravelli, Stefano Fagioli (Indriolo et al. 2011)

1. What are the commonalities in the pathobiology between IBD and periodontitis?

a. Is the role of bacteria in IBD similar to that in periodontitis?

There are similarities in both chronic inflammatory diseases in regards to the likely role of commensal bacteria in eliciting a host tissue inflammatory response. The role of a specific group of putative pathogens is probably different when comparing both diseases. In IBD, there is no evidence that a specific pathogen (e.g. *Mycobacterium paratuberculosis* as it was initially hypothesized) has any etio-pathogenic role in triggering the disease events. In contrast, in Periodontitis there is a group of putative pathogens with a defined set of virulence factors that have been associated with disease.

Is the role of the host response in IBD similar to that in periodontitis? There are also similarities in both chronic inflammatory diseases in regards to the host response. Ulcerative colitis (UC) is characterized by a Th-2 response with a prevalent overproduction of IL-13. In contrast, Crohn's disease (CD) is characterized by a Th-1 response with overproduction of IFN-gamma. In periodontal diseases, both responses have been suggested to play a role, with a Th-1 response more related to gingivitis and a Th-2 to periodontitis. In IBD, an intrinsic dysregulation of the gut epithelial innate immune responses has been reported with different expression of Toll-like receptors. In periodontitis, this dysregulation has not been reported, although there is evidence that specific periodontal pathogens may alter the expression of these receptors.

b. Is the role of genetic and environmental factors in IBD similar to that of periodontitis?

Twin studies provide evidence of genetic predisposition for UC, although

the specific responsible genes have not been identified. In CD, however, an association with a CARD 15 gene variant has been demonstrated, with carrier frequencies of one or more variant CARD 15 alleles (SNPs) between 22% and 60% of the subjects. This mutation of the NOD2/CARD15 (Caspase Recruitment Domain) gene impairs the ability to recognize bacterial components of the commensal intestinal microbiota and triggers an inadequate immune response. Twin studies also provide evidence of genetic susceptibility for periodontitis, and several SNPs have been associated with its prevalence and severity, but the data is not consistent across different populations.

Smoking is a common risk factor for both CD and periodontitis.

2. What is the epidemiological evidence for an association between IBD and periodontitis?

Oral conditions such as pyostomatitis vegetans, gingival hyperplasia, papillomatosis of the oral mucosa, vesicular eruptions, periodontitis and caries have been linked to IBD, specifically to CD. The evidence of a specific association between IBD and periodontitis is scarce. There is a case control study reporting a significant association between UC or CD and periodontitis (Brito et al. 2008) and a

recent cross-sectional study (Stein et al. 2010) demonstrating a positive, although weak association between CD and periodontitis. Conversely, another case-control study (Grössner-Schreiber et al. 2006) did not find an association with periodontitis.

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